Overview of the Rodenticide Comparative Ecological Assessment

January 16, 2003

Introduction

This "Overview" summarizes EPA's preliminary comparative assessment of potential rodenticide risks to birds and nontarget mammals. Upon issuance of the rodenticide cluster and zinc phosphide REDs in 1998, EPA noted that recent information had come to the Agency's attention regarding potential adverse effects to birds and non-target mammals. As noted in the 1998 Rodenticide Cluster RED, EPA planned to further evaluate these potential risks to determine if additional risk mitigation is indicated prior to concluding that uses are eligible for reregistration. Following an October, 1999, public meeting at which EPA presented a comparative approach for evaluating potential risks, EPA decided to use a public participation process to ensure broad stakeholder input on the ecological assessment and any resulting mitigation options.

The assessment, "Potential Risks of Nine Rodenticides to Birds and Nontarget Mammals: a Comparative Approach", dated December 19, 2002, and additional supporting documents are available on the internet and in the pesticide docket for public viewing. The primary focus of the assessment is to compare and rank potential risks of nine[1,2] rodenticide active ingredients. The purpose of this summary is to assist the reader by identifying the key features and findings of the assessment and to enhance understanding of the conclusions reached in the assessment. The nine rodenticides in this ecological assessment include those addressed in the Reregistration Eligibility Decisions (REDs) for the Rodenticide Cluster (brodifacoum, bromadiolone, bromethalin, chlorophacinone, diphacinone,) and zinc phosphide, as well as three other rodenticides (warfarin, difethialone, and cholecalciferol). EPA notes that this is the preliminary comparative assessment which may be refined and/or revised significantly based on comments or additional data. The data and information used to derive these risk estimates are discussed in detail in the comparative ecological assessment document.

Uses

Type of Pesticides:

- 1st generation anti-coagulants (diphacinone, chlorophacinone, warfarin)

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1 While there are 11 actual rodenticides, the sodium salt of warfarin, which only includes a single indoor product, has been lumped with warfarin, and the sodium salt of diphacinone, which only includes two indoor products, has been lumped with diphacinone.

2 The Rodenticide Cluster RED also mentioned two (2) other rodenticides (pival and its sodium salt) that were not eligible for re-registration in 1998.

- 2nd generation anticoagulants (brodifacoum, difethialone, bromadiolone)[3]
- Non-anticoagulants [zinc phosphide, bromethalin, cholecalciferol (Vitamin D_3)]

3 Second-generation anticoagulants are anticoagulant compounds believed to be effective in controlling commensal rats or mice that are resistant to warfarin and/or other anticoagulant rodenticides, which now are called "first-generation anticoagulants".

Types of Uses:

- The predominant use of these rodenticides is for control of commensal rats and mice (Norway rat, roof rat, and house mouse) at structural sites (in and around buildings, inside of transport/cargo vehicles and in sewers).
- The remaining uses are for control of rodents, rabbits, and mongoose at non-structural sites [e.g., terrestrial food/feed (sugarcane, rangeland, vineyards) terrestrial non-food/non-feed (irrigation ditches, forestry, orchards, groves, reduced tillage and non-till corn)].

Types of Applicators:

- General-use and restricted-use products exist.
- Most products with structural sites on their labels are classified as general-use products.
- Most products with non-structural sites on their labels are classified (or have been proposed to be classified) as "Restricted Use Pesticides". Only certified applicators or persons under their direct supervision may apply these products.

Types of End-Use Formulations:

- The majority of products are dry bait (meal, pellet, and block) formulations.
- There are three liquid bait formulations.
- There are three tracking powder formulations.

Types of Application Methods:

- Products used at structural sites are applied by hand.
- Products used at non-structural sites are applied by hand placement or using hand-held equipment, though ground and aerial equipment may be used to apply selected field-use products.
- Timing and rates of application vary from product to product.

Environmental Fate and Effects

The methodology used in this ecological assessment is similar to that used in the Agency's "Comparative Analysis of Acute Risk From Granular Pesticides" and "A Comparative Analysis of Ecological Risks from Pesticides and Their Use: Background, Methodology, Case Study"; both of these assessments were reviewed by a FIFRA Scientific Advisory Panel in December 1998. For this assessment risk conclusions are based on a "weight-of-evidence" approach, and data also are compared and evaluated by means of a comparative analysis model (a simple multi-attribute rating technique). Each rodenticide is ranked according to potential for overall risk to birds and mammals, primary risk to birds, primary risk to nontarget mammals, secondary risk to birds (avian predators and scavengers), and secondary risk to mammals (mammalian predators and scavengers).

Risk, Exposure, and Uncertainty

Risk is a function of exposure and hazard (toxicity). Data are available to estimate toxicity based on laboratory acute and secondary toxicity tests. Typical use information used to estimate nontarget organism exposure, such as amount of rodenticide active ingredient or formulated product applied per unit area, is not available. Thus, exposure estimates are largely based on the amount of active ingredient available per kilogram of the grain bait formulation (mg ai/kg-bait).

There are many factors which influence which nontarget animals might be exposed to rodenticide baits. They would include the species found in and near the treatment areas, species feeding habits, their home range, their propensity to feed in and near human buildings, the availability of the bait, etc. Of great importance is that many nontarget organisms are attracted to and consume grain-based baits. In addition, nontarget predators and scavengers also feed on rats, mice or other target species, and they are not likely to avoid feeding on those that have eaten rodenticide bait.

Labeled concentrations of the rodenticides were used to estimate acute primary exposure, i.e., to estimate the amount of bait and number of bait pellets that birds and mammals of various sizes need to consume in a single feeding to obtain a dose expected to be lethal to 50% of the individuals in the population (i.e., LD_{50} dose). Estimates of food-ingestion rates came from established allometric equations.

Estimates of acute primary exposure were not useful as estimates of secondary exposure. Such exposure estimates are more complex and require consideration of residues in tissues of target organisms that are commonly consumed by predators and scavengers, knowledge of what residue level will result in mortality, and how long residues last in tissues. Laboratory tests using predators and scavengers to test for mortality due to secondary exposure were available. Design and methods varied considerably adding variability to the results and to the analysis. Pending standardization of methods and requirements, however, they provide the best data available. The mean percent (%) mortality for these bird and mammal laboratory tests were used to estimate both secondary exposure and risk. In addition, retention time in tissues consumed by scavengers and predators were also factored into secondary exposure and risk estimates.

Retention time is not a direct measure of effect for secondary risk to birds and mammals, but it is an important contributing factor. The combination of mean % mortality from secondary laboratory toxicity studies, which characterizes the secondary toxicity from short-term exposures, and available data on retention time in both blood and liver, which indicates how long toxic levels can persist in target animal tissues, can characterize the secondary risk to birds and mammals. A discussion of potential lethal residue levels in tissues is included in the assessment, but there are uncertainties in establishing such levels in most nontarget organisms.

In preliminary pesticide assessments the assumption is made that nontarget birds and mammals are likely to be exposed to the pesticide without attempting to establish a quantitative measure of this likelihood. The existence of substantial incident data along with liver residues provides some important support for the assumption that nontarget birds and mammals are exposed and adversely affected by the use these rodenticide baits. The fact that numerous species have been found exposed to these rodenticide formulations, including predators and scavengers, indicates that both primary and secondary exposures are occurring.

Additional data to fill-in where data is missing or to standardize data where the quality is variable, as well as specific use and exposure information, will likely provide the greatest reduction in uncertainty for these analyses. Some concerns about adverse sub-lethal effects can be addressed through avian reproduction studies, which the Agency will require for all pesticides with outdoor uses. The no-observable-adverse-effects concentration (NOAEC) established from these studies will be a more appropriate indicator of a toxicity threshold than is the liver residue in dead animals.

Comparative Risks to NonTarget Birds and Mammals - Using the Comparative Analysis Model

The available information indicates that differences exist among these rodenticides in their potential risks to birds and nontarget mammals. Using the available information and the comparative analysis model, each rodenticide is ranked according to potential for overall risk to birds and mammals. The overall risk to birds and mammals represents the summary of the following types of risks: primary risk to birds, primary risk to nontarget mammals, secondary risk to birds (avian predators and scavengers), and secondary risk to mammals (mammalian predators and scavengers). The summary scores for each type of risk were calculated by rating each alternative rodenticide on one or more measures of effect for the type of risk, and assigning the each measure of effect an importance value (generally all were of equal importance). Then, a summary score for each alternative rodenticide is calculated as a weighted average of the ratings, where the weights (0 to 10) represent the relative importance of the measure of effect for each type of effect. The higher the resultant summary score, the higher the potential risk for that rodenticide and that type of risk. The summary scores range from 10.00 (high) to 0.00 (low).

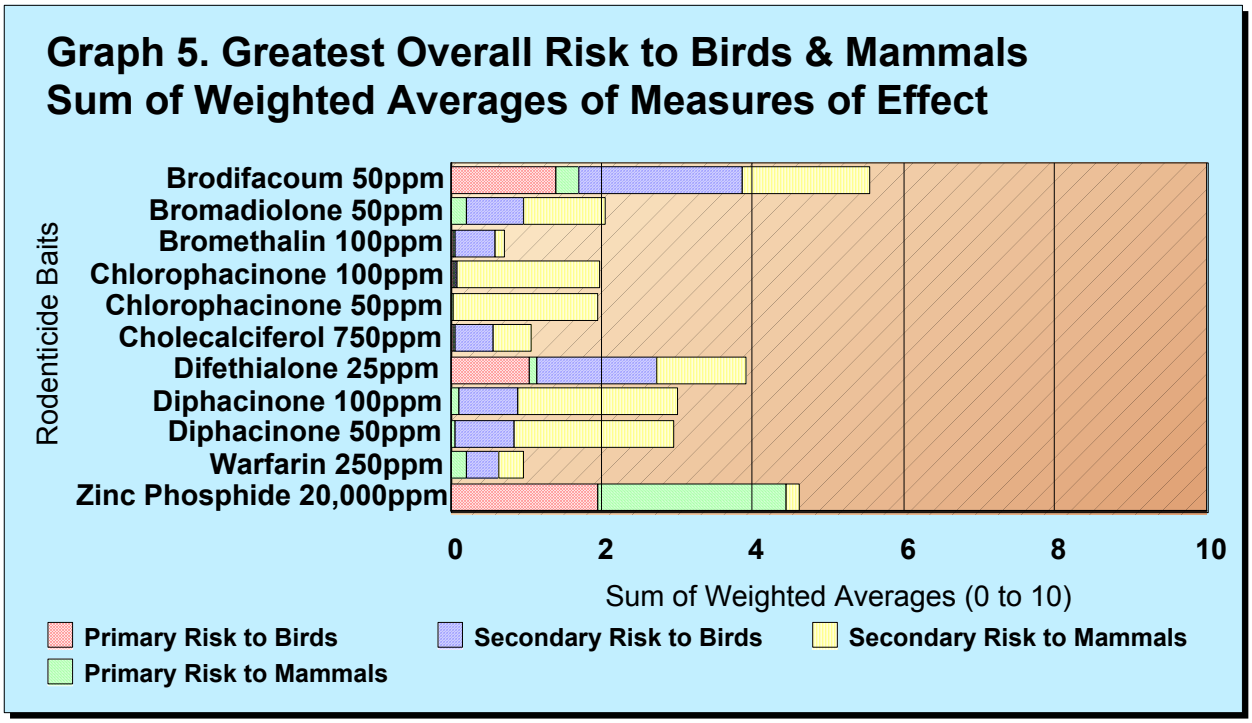
The results of this comparative analysis show that brodifacoum, zinc phosphide, and difethialone are ranked as the rodenticides posing the greatest potential overall risk to nontarget birds and mammals (Table 1, Figure 1).

Table 1. Comparative Analysis Model Results for Overall Risk to Birds and Mammals. Tabulated values are weighted measures of effect.

Rodenticide	bait ai (ppm)	Primary risks		Secondary risks		Summary values
		birds	mammals	birds	mammals	
Brodifacoum	50	5.58	1.25	8.60	6.76	5.55
Bromadiolone	50	0.10	0.71	3.03	4.40	2.06
Bromethalin	100	0.10	0.10	2.20	0.44	0.71
Chlorophacinone	100	0.14	0.16	0.03	7.62	1.99
Chlorophacinone	50	0.07	0.08	0.03	7.62	1.95
Cholecalciferol	750	0.12	0.18	2.00	2.00	1.07
Difethialone	25	4.15	0.45	6.29	4.82	3.93
Diphacinone	100	0.01	0.43	3.18	8.42	3.01
Diphacinone	50	0.01	0.22	3.18	8.42	2.96
Warfarin	250	0.04	0.83	1.72	1.32	0.98
Zinc Phosphide	20,000	7.81	10.00	0.00	0.69	4.63

A sensitivity analysis is performed to identify the most sensitive measure of effect(s) and to determine if changes of 50% or more in the sensitive measures of effect would change the results of the analysis. The results of this analysis indicates that the comparative model rankings are robust, especially for brodifacoum, zinc phosphide and difethialone. Their ranking as the three rodenticides posing the greatest overall potential risk do not change when values for the measures of effect are varied by $\pm$50%.

Figure 1. Comparative Analysis Model Summary Values For Overall Risks to Birds and Nontarget Mammals (Graph 5 was extracted from the Agency's preliminary ecological assessment entitled: "Potential Risks of Nine Rodenticides to Birds and Nontarget Mammals: a Comparative Approach").



Comparative Risks to NonTarget Birds and Mammals - Using the Weight-of-Evidence Approach

Considering all data and supporting information available a "weight-of-evidence" analysis is performed where each rodenticide is assigned a rating of high, moderate, or low for potential primary risk to birds, primary risk to nontarget mammals, secondary risk to birds, and secondary risk to mammals (Table 2). Differences among the rodenticides in their potential primary and secondary risks to birds are pronounced. Not surprisingly, all the rodenticides pose a high potential risk to nontarget mammals, while the potential primary risks to birds are highest for zinc phosphide, brodifacoum, and difethialone. Brodifacoum, difethialone, bromadialone, diphacinone and chlorophacinone present a greater potential risk to raptors and avian scavengers than do the other rodenticides. Zinc phosphide potentially poses minimal risks to either predatory birds or mammals, but insufficient data are available for bromethalin and cholecalciferol. Finally, brodifacoum, and possibly difethialone baits may present the highest potential overall risks to birds and nontarget mammals.

Table 2. Primary and Secondary Risk Presumptions For Birds and Nontarget Mammals

Rodenticide	Primary risks		Secondary risks	
	birds	mammals	birds	mammals
Second-generation anticoagulants				
Brodifacoum	high	high	high	high
Difethialone	high	high	high	high
Bromadiolone	low to moderate	high	moderate	high
First-generation anticoagulants				
Diphacinone	low	high	moderate	high
Chlorophacinone	low to moderate	high	low	high
Warfarin	low	high	low	moderate
Others (non-anticoagulants)				
Bromethalin	moderate to high	high	insufficient data available	
Zinc phosphide	high	high	low	low
Cholecalciferol	low to moderate	high	insufficient data available	

Supporting Information

The following paragraphs present some of the information that was considered and used in both the comparative analysis model and the weight-of evidence approach to ranking the rodenticides based on potential risk to birds and mammals. The information is presented based on the different mode of actions of the rodenticides.

Second-generation anticoagulants

The second-generation anticoagulants (brodifacoum, difethialone, bromadiolone) tend to be very highly toxic to birds and mammals. A 100-g bird can potentially ingest an LD_{50} dose by consuming as few as three to five bait pellets of brodifacoum or difethialone. A single brodifacoum bait pellet weighing 0.26 g provides more than an LD_{50} dose for a 25-g bird. Bromadiolone is less acutely toxic, and birds are not likely to ingest a lethal dose of bait in a single feeding. Risk quotients (RQs) for dietary exposure greatly exceed the Agency's level of

concern (LOC) (RQ $\geq$ 0.5) for risk to birds from brodifacoum (RQs = 25 to 63) and difethialone (RQs = 18 to 50). The dietary LOC for bromadiolone is exceeded slightly (RQs = 0.3 to 1.4). All three compounds are very highly toxic to rats. A 100-g nontarget mammal could ingest an LD_{50} dose by consuming as few as four to eleven bait pellets of any second-generation anticoagulant.

Based on findings from secondary toxicity tests, field trials, and control programs, brodifacoum is much more highly toxic secondarily to birds than is any other rodenticide. Of 149 individuals exposed to brodifacoum-poisoned prey in laboratory studies, 42% died and about one-third of the
survivors displayed signs of poisoning, such as bleeding or prolonged blood-coagulation times. In contrast, no other rodenticide killed more than 9% of the test birds, and some killed none. Deaths of owls, falcons, harriers, gulls, and skuas have been reported after brodifacoum applications in the field. Based on secondary toxicity tests and information from the field, both brodifacoum and bromadiolone appear to pose high risks to mammalian predators and scavengers that feed on poisoned target species. Little information is available for difethialone; however, secondary risks are likely comparable to those posed by brodifacoum because the two compounds are similar in chemical structure, physical/chemical properties, and acute toxicity.

Second-generation anticoagulants circulate for days in the blood of exposed birds and mammals and are stored and persist in numerous body tissues for much longer than other rodenticides. Brodifacoum has been detected in the liver of possums nine months after administration of a sublethal dose, and a half-life of up to 350 days has been reported in rats sublethally dosed. Bromadiolone and difethialone have retention times comparable to those of brodifacoum. Bioaccumulation in predators and scavengers seems likely for those that survive repeated feeding on target species exposed to these compounds, even if repeat exposures occur weeks or even months after initial exposure.

The Agency is aware of 258 incidents in which one or more of the nine rodenticides were detected in birds or nontarget mammals. Brodifacoum residue was detected in 192 (74%) incidents, including 22 of 23 involving exposure to more than one rodenticide. Quantitatively, brodifacoum accounts for most over-the-counter sales to the general public, which may partially explain the high number of recorded incidents. Bromadiolone was detected in 37 incidents, but 17 of those also involved exposure to brodifacoum. Difethialone has been detected in one dead animal, a bobcat. Birds found dead with second-generation anticoagulant residue in the liver include great horned owls, red-tailed hawks, other species of owls and hawks, golden eagles, corvids, and others. Mammals with residue of second-generation anticoagulants include coyotes and foxes (including 9 endangered kit foxes), bobcats, a mountain lion, raccoons, skunks, opossums, several deer, numerous tree squirrels, and others.

First-generation anticoagulants

The first-generation anticoagulants are less acutely and secondarily toxic to birds than are the second-generation compounds. Birds are not likely to ingest enough pellets in a single feeding to obtain an LD_{50} dose of any first-generation anticoagulant. Only chlorophacinone (RQs = 0.9 to 1.8) exceeds the dietary level of concern for birds. Based on pen tests, warfarin appears to

pose less risk to birds than do other anticoagulants, especially brodifacoum, difethialone, and bromadiolone. Risk to small mammals is expected for all rodenticides, but first-generation compounds are less likely than second-generation compounds to provide an LD_{50} dose in a single feeding.

Mammals appear to be at greater secondary risk to first-generation anticoagulants than are birds that feed on animals that have eaten bait. In secondary toxicity tests, diphacinone and warfarin displayed comparable toxicity to bromadiolone (8-9% mortality) but much less than that for brodifacoum. None of 106 predatory birds died after exposure to chlorophacinone-only poisoned prey. In contrast, mortality to mammals exposed to diphacinone- and chlorophacinone-exposed prey was extensive (55-58% mortality). Mortality of mammals due to warfarin exposure was considerably less (9%) than for the other anticoagulants. Little information regarding secondary risks in the field is available for any of the first-generation compounds.

Considerably fewer toxicokinetic data are reported for the first-generation anticoagulants than for the second-generation anticoagulants. The available information indicate that warfarin and chlorophacinone may be much more rapidly eliminated from the body than are second-generation compounds and possibly diphacinone. Most evaluations of risk take little account of these implications. In field settings, multiple exposures to warfarin or chlorophacinone, even weeks or months apart, may not necessarily lead to increased risk. In contrast, bioaccumulation of the more persistent anticoagulants may increase the risk of death or other adverse effects.

First-generation anticoagulants have been implicated in 32 (14%) of the 258 reported rodenticide incidents, although 10 of those also involved exposure to brodifacoum and/or bromadiolone. Diphacinone was detected in 18 incidents and chlorophacinone in 10 incidents. Four incidents were reported for warfarin.

Others (non-anticoagulants)

The non-anticoagulants differ considerably in their potential primary risks to birds and mammals. Zinc phosphide potentially poses a very high risk to both birds and nontarget animals that eat bait, although some birds may be less susceptible than others. A bird or mammal can potentially ingest several LD_{50} doses in a single feeding. Dietary risk also is high (RQs = 7-43). Cholecalciferol exhibits some avian dietary risk (RQs = 0.6-1.4) from repeat feedings, but birds are not likely to ingest a lethal dose in a single feeding. An LD50 dose of bromethalin could be ingested in about six bait pellets for a 25-g bird and 23 pellets for a 100-g bird.

Secondary risks appear to be low for zinc phosphide, but few data are available to assess the risks from bromethalin and cholecalciferol. Zinc phosphide-poisoned prey caused the deaths of only three of 77 mammals and none of 19 birds of prey exposed in 15 studies. Some animals regurgitated prey and others refused to consume gastro-intestinal tracts (GIT). Almost all zinc phosphide detected in the carcass of animals that died from eating bait was in the GIT, likely as undigested bait. Dogs and feral house cats survived after eating cholecalciferol-poisoned rats or possums in New Zealand; signs of toxicosis were reported in the dogs but did not persist. Three

birds of prey survived with no apparent adverse effects after feeding for 10 days on rats poisoned with cholecalciferol. Less information is available for bromethalin. As a result, insufficient data are available for both cholecalciferol and bromethalin (Table 1) to make risk presumptions for birds and nontarget mammals.

Zinc phosphide poisoning is suspected in 23 rodenticide incidents, most involving wild turkeys or geese. The Agency is not aware of any wildlife incidents with bromethalin or cholecalciferol, but that might be due to inadequate detection methods or failure of testing laboratories to include these compounds in pesticide screens.

Public Participation

Release of the rodenticide comparative ecological assessment to the public docket and internet (www.epa.gov/pesticides/rodenticidecluster) will be announced in the *Federal Register*. In addition to providing comments directly to the Rodenticide Cluster and Zinc Phosphide docket, the public is invited to contact John Pates, the Chemical Review Manager for the Rodenticide Cluster and Zinc Phosphide at (703) 308-8195 with questions or comments you would like to bring to the Agency's attention. It is further noted that the Agency will be considering possible refinements to the assessment, benefits (including public health), risk-mitigation options, and other issues following the 60-day public comment period. Interested stakeholders are further encouraged to follow the development of the Amended Rodenticide Cluster Reregistration Eligibility Decision (RED), by monitoring entries to the public docket. Prior to finalizing amendments to the 1998 Rodenticide Cluster RED, the Agency, in cooperation with USDA, will hold a conference call with interested stakeholders outlining the risk mitigation measures the Agency determines are necessary.